

# Rosiglitazone (Avandia) and rosiglitazone with metformin (Avandamet) for type 2 diabetes mellitus

(rosey–GLI–tah–zone)

## Summary

- Rosiglitazone improves glycaemic control but there is a lack of evidence that it improves diabetes-related clinical complications and mortality. Prescribers should consider this — along with recently emerging safety information — when assessing the ratio of potential harms and benefits for each patient.
- Rosiglitazone is no longer indicated in combination with insulin or for triple oral therapy in combination with metformin and a sulfonylurea.
- Rosiglitazone is a third-line choice. It may still be considered as part of dual therapy when either metformin or a sulfonylurea is contraindicated or not tolerated.
- Insulin should also be considered instead of rosiglitazone in these scenarios.
- Do not use rosiglitazone in people with heart failure or a history of heart failure.
- Avoid using rosiglitazone in people with ischaemic heart disease. Take particular care when prescribing the drug to people with a high risk of cardiovascular events.
- Bear in mind the possibility that rosiglitazone may increase the risk of a myocardial infarction.
- A large clinical trial found an increased rate of fractures of the upper arm (humerus), hand and foot among women using rosiglitazone.
- Wait 8 weeks before increasing the dose, as the full effect of the drug may not be seen before this time. In clinical trials of glitazone treatment, 25% to 30% of patients had no improvement in glycaemic control.
- Establish the effective and tolerated dose of each component as single drugs before considering the rosiglitazone with metformin combination tablet. Do not use combination tablets for patients taking more than 2 g/day of metformin because the maximum recommended daily dose of rosiglitazone will be exceeded.

## PBS listing

### Authority required

Rosiglitazone (Avandia) can be used in patients with type 2 diabetes whose blood glucose concentrations are inadequately controlled ( $HbA_{1c} > 7\%$ ) as dual oral therapy with metformin or a sulfonylurea when combination therapy with metformin and a sulfonylurea is contraindicated or not tolerated.

Rosiglitazone is no longer PBS listed for initiation of triple oral therapy (that is, in combination with metformin and

a sulfonylurea). The PBS will continue to subsidise continuing treatment with rosiglitazone for people currently stabilised on this combination until **1 February 2009**. As of this date rosiglitazone will not be subsidised for triple oral therapy.

Rosiglitazone is no longer PBS listed in combination with insulin, either for initiation or continuing use. Patients currently using both rosiglitazone and insulin should be contacted as soon as possible to review their treatment regimen.

Rosiglitazone **is not** PBS listed as monotherapy.

## Authority required

Rosiglitazone with metformin combination tablets (Avandamet) can be used in patients with type 2 diabetes whose blood glucose concentrations are inadequately controlled ( $\text{HbA}_{1c} > 7\%$ ) with metformin, and a sulfonylurea is contraindicated or not tolerated.

Rosiglitazone with metformin combination tablets **are not** PBS listed for use in combination with insulin.

## Reason for PBS listing

Rosiglitazone was recommended for listing by the Pharmaceutical Benefits Advisory Committee (PBAC) as dual oral therapy with metformin or a sulfonylurea on a cost-minimisation basis compared with insulin.<sup>1</sup>

Rosiglitazone with metformin combination tablets were recommended for listing by the PBAC on the grounds that the combination tablets were no worse than concomitant rosiglitazone and metformin.<sup>2</sup>

## Listings for triple oral therapy and combination with insulin removed

The listings for triple oral therapy and combination with insulin were removed from the PBS in late 2008. This followed changes to the TGA-approved indications for rosiglitazone after a further review of existing data about the safety of rosiglitazone (see Place in therapy and Safety issues).<sup>3, 4\*</sup>

## Place in therapy

Rosiglitazone is a thiazolidinedione ('glitazone') antidiabetic drug that should be considered a third-line choice. Metformin (or, when this is contraindicated, a sulfonylurea) is usually the drug of first choice for type 2 diabetes.

When combination therapy is required, metformin and a sulfonylurea is the combination of first choice.

Rosiglitazone can be considered when either metformin or a sulfonylurea is contraindicated or not tolerated.<sup>5</sup>

Insulin should also be considered instead of rosiglitazone in these scenarios.

\*The PBAC reviewed the listing for pioglitazone at its November 2008 meeting in light of the changes to the TGA-approved indications for rosiglitazone. The outcome of this review was not publicly known at the time of writing.

## Rosiglitazone's effect on morbidity and mortality is uncertain

Most of the clinical trials of rosiglitazone have measured surrogate outcomes such as effects on  $\text{HbA}_{1c}$  levels, lipids or insulin sensitivity and were not long term. As such, there is a lack of evidence that rosiglitazone improves diabetes-related clinical complications and mortality.<sup>6</sup> One large trial is in progress comparing the cardiovascular outcomes of patients with type 2 diabetes using rosiglitazone and metformin or a sulfonylurea with those of patients using metformin and a sulfonylurea.<sup>7</sup>


## Lifestyle changes remain important


Healthy eating, exercise, weight loss and smoking cessation reduce cardiovascular risk and improve glycaemic control in people with diabetes. If glycaemic control has deteriorated, assess the patient's adherence to lifestyle changes and reinforce their importance as adjunctive therapy.

## Metformin with a sulfonylurea is the combination of first choice

Metformin improves glycaemic control and reduces the incidence of macrovascular complications and death among patients with type 2 diabetes.<sup>8</sup> The sulfonylureas and insulin improve glycaemic control and reduce the incidence of microvascular complications in diabetes.<sup>9</sup>

Metformin plus a sulfonylurea is the preferred combination because of evidence that it reduces diabetic complications, because it is probably more cost-effective and because clinicians have many years of experience using these agents.

Metformin is contraindicated in people with severe renal impairment or other risk factors for lactic acidosis. It may also cause gastrointestinal adverse effects such as diarrhoea, nausea and abdominal bloating, but these are often transient and it is not usually necessary to stop the drug.<sup>10</sup> [www](#) 

[www](#)  Consult the *Australian Medicines Handbook* or refer to this review at [www.npsradar.org.au](http://www.npsradar.org.au) for additional information about contraindications and intolerance to metformin.

Hypoglycaemia is the most common adverse effect with sulfonylureas but can be minimised by splitting or reducing the daily dose. The elderly are at greater risk of hypoglycaemia, so shorter-acting agents such as gliclazide or glipizide are preferred.

Both rosiglitazone and the sulfonylureas are associated with weight gain so patients should not be switched to rosiglitazone because of this adverse effect.

### Rosiglitazone with metformin as a fixed-dose combination tablet

For people already stabilised on rosiglitazone and metformin, rosiglitazone with metformin combination tablets can be considered if there is an equivalent strength of the combination tablet. Combination tablets should not be used to initiate therapy for diabetes in patients who have not previously used an oral antidiabetic.

### Rosiglitazone is no longer approved for triple oral therapy

Rosiglitazone is no longer approved for use in combination with metformin and a sulfonylurea (i.e. triple oral therapy) because of an increased risk of heart failure.<sup>11</sup> The PBS will subsidise rosiglitazone for people stabilised on triple oral therapy that includes rosiglitazone until 1 February 2009. As of this date rosiglitazone will not be subsidised for triple oral therapy.

If dual therapy with metformin and a sulfonylurea fails, consider adding insulin, as it reduces the risk of diabetes complications.<sup>9</sup> Do not delay introducing insulin when oral drug therapy no longer controls blood glucose.

For information on initiating insulin see *NPS News 56: Managing hyperglycaemia in type 2 diabetes* at [www.nps.org.au](http://www.nps.org.au).

Other third-line oral antidiabetic drugs include pioglitazone<sup>†</sup>, repaglinide (not PBS listed), sitagliptin or acarbose but the long-term benefit–harm profiles of these drugs are yet to be established. See the *NPS RADAR* reviews of pioglitazone and sitagliptin at [www.nps.org.au](http://www.nps.org.au) for further information on these agents.

### Do not combine rosiglitazone and insulin

Do not start or continue rosiglitazone in people using insulin, because of the increased risk of congestive heart failure, weight gain and oedema (particularly at a daily dose of 8 mg).<sup>12</sup> Meta-analyses from both the US Food and Drug Administration and the manufacturer showed a trend towards a doubling of the risk of an ischaemic event or heart failure when rosiglitazone was combined with insulin (compared with adding placebo to insulin).<sup>11,13</sup>

### Safety issues

Do not prescribe rosiglitazone for people with an acute coronary syndrome, heart failure of any severity (New York Heart Association [NYHA] Class I–IV) or a history of heart failure. [www](#)

Avoid using rosiglitazone in people with ischaemic heart disease and take particular care when prescribing it to people with a high risk of cardiovascular events.

Hypoglycaemia is uncommon with rosiglitazone alone but may occur when it is combined with a sulfonylurea; adjust the dose of sulfonylurea to reduce the risk of hypoglycaemia (see Dosing issues).

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website ([www.tga.gov.au](http://www.tga.gov.au)).

[www](#) Refer to this review at [www.npsradar.org.au](http://www.npsradar.org.au) to see the New York Heart Association grading of heart failure.

<sup>†</sup> The PBAC reviewed the listing for pioglitazone at its November 2008 meeting in light of the changes to the TGA-approved indications for rosiglitazone. The outcome of this review was not publicly known at the time of writing.

## Rosiglitazone may increase risk of cardiovascular events

Do not prescribe rosiglitazone to people with ischaemic heart disease. Take particular care when prescribing the drug to people with a high risk of cardiovascular events.

Recent meta-analyses, including one performed by the manufacturer, have raised concerns about a potential increase in risk of myocardial ischaemia among people treated with rosiglitazone.<sup>11,13–15</sup> The risk appears greater for people taking rosiglitazone in combination with insulin or in those taking nitrates.<sup>11,13</sup> While 3 large randomised trials (some of which were included in some of the meta-analyses) did not report a significant increase in the risk of myocardial infarction, their wide confidence intervals do not rule out such a risk.<sup>16–18</sup>

Some additional information on rosiglitazone is provided by 3 large studies of the impact of intensive glucose lowering on cardiovascular outcomes in people with type 2 diabetes with, or at high risk of, cardiovascular disease. None of these studies specifically investigated the effect of rosiglitazone on cardiovascular outcomes, so no clear conclusions about its use can be made.

The ACCORD trial found a significant increase in all-cause mortality and death from cardiovascular causes in the intensive treatment arm compared with standard treatment.<sup>19</sup> The ADVANCE trial did not find an increased risk of cardiovascular events or all-cause mortality.<sup>20</sup> Rosiglitazone use was more common in the ACCORD trial (91% in the intensive treatment arm and 57% in the standard treatment arm) than in the ADVANCE trial (fewer than 20% in both arms). However, a post-hoc analysis did not identify rosiglitazone as contributing to the increased mortality seen in the ACCORD study<sup>19</sup> and the different results in the ADVANCE and ACCORD trials might be due to differences in baseline HbA<sub>1c</sub>, the different blood glucose targets (ACCORD: HbA<sub>1c</sub> < 6.0% vs ADVANCE: HbA<sub>1c</sub> < 6.5%) or the pace of glucose lowering, rather than differences in glitazone use.<sup>20</sup>

The third trial, the Veterans Affairs Diabetes Trial (VADT), is yet to publish its results.

The possibility of increased cardiovascular risk with rosiglitazone should be borne in mind until further evidence becomes available.

For further information see the NPS fact sheet *Rosiglitazone and cardiac risk* (available at [www.nps.org.au](http://www.nps.org.au)).

## Fluid retention, peripheral oedema and the risk of heart failure

Rosiglitazone **should not be used** in patients with heart failure (NYHA I–IV) or a history of heart failure.<sup>12</sup> The risk of new or exacerbated heart failure increases in people with type 2 diabetes taking rosiglitazone.<sup>15,18</sup>

Diabetes is a risk factor for heart disease and congestive heart failure.<sup>21</sup> Glitazones are associated with fluid retention and oedema that could exacerbate existing heart failure or precipitate it in people at risk.<sup>6,22</sup>

Oedema is more common when glitazones are used in combination therapy (3% to 6% of patients in rosiglitazone trials) and most likely when glitazones are used with insulin (13% to 16% when rosiglitazone is combined with insulin).<sup>21,23</sup>

Assess risk factors for heart failure before prescribing glitazones — both medical (e.g. history of heart failure, myocardial infarction or coronary heart disease; hypertension; left ventricular hypertrophy; age > 70 years; diabetes for > 10 years) and pharmacological (e.g. use of nonsteroidal anti-inflammatory drugs, calcium-channel blockers, insulin).<sup>21</sup>

Prescribers and patients should be alert for symptoms of developing heart failure. Checking weight daily can provide an early warning of fluid accumulation.

## Weight gain is a problem

Weight gain is associated with all glitazones and is dose dependent.<sup>24</sup> Gains of up to 5 kg were seen in clinical trials<sup>6</sup> and even greater gains occurred when rosiglitazone was combined with sulfonylureas.<sup>24</sup>

Weight continued to increase for as long as data were recorded in trials (up to 84 weeks).<sup>25</sup> Reinforce the importance of lifestyle measures in limiting weight gain caused by medications.

## Rosiglitazone appears to increase the risk of peripheral fractures among women

A significantly greater risk of fracture in women taking rosiglitazone has been reported in 1 large clinical trial (n = 4360). The prevalence of fractures among women taking rosiglitazone was 9.3%, compared with 5.1% of women taking metformin (relative risk [RR] 1.83, p < 0.01) and 3.5% of women taking glibenclamide (RR 2.68, p < 0.01).<sup>16</sup> Fractures were most common in the upper arm (humerus), hand and foot.

Decreases in hip bone mineral density (BMD) have been reported in non-diabetic postmenopausal women during a 14-week randomised trial of rosiglitazone (n = 50).<sup>26</sup> One observational study has suggested that the glitazones may cause bone loss among elderly women but not elderly men.<sup>27</sup>

### Glitazones may cause or worsen macular oedema

A small number of postmarketing reports have suggested that there may be an association between the glitazones and the development or worsening of diabetic macular oedema, resulting in a decrease in visual acuity.<sup>12,28</sup> Any changes in vision reported by patients taking rosiglitazone should be investigated.

### Remain vigilant for signs of liver toxicity

The first available glitazone, troglitazone, was withdrawn because of liver toxicity. The risk appears to be significantly lower with rosiglitazone but several case reports exist for both rosiglitazone and pioglitazone, including elevated liver enzyme levels, hepatocellular damage, hepatitis and liver failure.<sup>25,29,30</sup>

Patients with liver disease (including increased transaminase levels > 2.5 times the upper limit of normal) should not be started on glitazone therapy.<sup>12,29</sup>

Glitazone-induced liver toxicity is unpredictable. Liver function tests are recommended before starting a glitazone and every 2 months for the first year, then periodically or when clinically indicated.<sup>31</sup> However, monitoring liver function should not be viewed as always identifying the problem effectively: in some cases of troglitazone liver toxicity, normal enzyme concentrations progressed to irreversible liver failure within 1 month.<sup>32</sup> If a patient presents with symptoms suggesting liver disease, this should be seriously considered and investigated.

### Drug interactions

No significant drug interactions have been reported with rosiglitazone. However, there is evidence that potential interactions could occur if rosiglitazone is combined with other drugs metabolised by the enzyme CYP2C8, such as rifampicin and trimethoprim (inducers of CYP2C8) and gemfibrozil (an inhibitor of CYP2C8).<sup>33</sup> Use caution if combining rosiglitazone with other drugs metabolised by CYP2C8. Ketoconazole may also interact with rosiglitazone.<sup>34</sup>

There is an increased risk of hypoglycaemia when rosiglitazone is combined with sulfonylureas or insulin.

Because they induce fluid retention, combining rosiglitazone with nonsteroidal anti-inflammatory drugs carries a potential increased risk of oedema and heart failure.<sup>30</sup>

Consult the *Australian Medicines Handbook* or the Avandia or Avandamet product information for more information about adverse effects.

## Dosing issues

The recommended dose of rosiglitazone is 4–8 mg/day. Patients should start at the lower dose of 4 mg/day, particularly those at risk of hypoglycaemia. Metformin should be titrated to the highest tolerable dose before starting rosiglitazone. Consider the rosiglitazone with metformin combination tablet only after the effective and tolerated dose of the individual components has been established. The available doses of rosiglitazone are shown in Table 1.

**Table 1: Dose strengths and appearance of rosiglitazone and rosiglitazone/metformin**

Doses	Tablet: colour, shape
<b>Rosiglitazone</b>	
4 mg	Orange, pentagonal shape
8 mg	Red–brown, pentagonal shape
<b>Rosiglitazone/metformin</b>	
2 mg/500 mg	Light pink, oval
2 mg/1000 mg	Yellow, oval
4 mg/500 mg	Orange, oval
4 mg/1000 mg	Pink, oval

Consider whether the available strengths of the combination tablets allow the appropriate dose of metformin to be given. Patients taking metformin doses of more than 2000 mg/day should not be prescribed the combination tablet, as the maximum recommended daily dose is rosiglitazone 8 mg / metformin 2000 mg.<sup>35</sup>

### Allow time for response before increasing dose

Rosiglitazone doses should not be increased before 8 weeks have elapsed; in most glitazone trials it has usually taken between 8 and 18 weeks for the full glycaemic response to be seen at any given dose. As HbA<sub>1c</sub> testing is recommended 3-monthly in patients whose therapy has changed or who are not meeting glycaemic goals, this seems an appropriate point to scrutinise the patient's response and consider if any modifications to therapy are necessary. If patients continue to show no effect after increasing the dose, rosiglitazone should be stopped.

A proportion of people does not respond to glitazone therapy with a decrease in fasting plasma glucose and/or HbA<sub>1c</sub> levels (primary treatment failure). The non-responder rate observed in clinical trials of glitazones was 25% to 30%.<sup>25</sup>

### Information for patients

Advise patients of emerging risks that may be associated with rosiglitazone. Advise patients that improvements in glycaemic control may take at least 8 weeks and ask them to:

- monitor for weight gain or ankle oedema
- report any symptoms of heart failure (such as breathlessness during daily activities)
- report signs of liver toxicity (nausea/vomiting, jaundice, dark urine, right upper abdominal discomfort).

For more detailed information about rosiglitazone, suggest or provide the Avandia consumer medicine information (CMI) or the Avandamet CMI (available at [www.nps.org.au](http://www.nps.org.au)).

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..... Updated July 2011: removal of streamlined PBS authority.

..... Updated October 2008: revocation of the triple therapy listing and addition of further contraindications.

..... Updated October 2007: fracture and cardiovascular risk, rosiglitazone with metformin combination tablet, use of insulin and rosiglitazone.

..... Updated June 2005: use in combination with insulin.

..... Updated February 2005: use in combination with metformin and a sulfonyleurea.

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